ORIGINAL ARTICLE

Formulation of Ondansetron HCl Matrix Tablets with Microenvironmental pH Modifier for Improved Dissolution and Bioavailability under Hypochlorhydria

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Abstract

Background: Ondansetron hydrochloride is a serotonin sub type-3 (5-hydroxytryptamine-3) receptor antagonist. It is a widely used drug for the treatment of post-operative nausea and vomiting (PONV) and chemotherapy-induced nausea and vomiting. The recommended oral dose regimen of ondansetron hydrochloride is 8 mg, three times a day up to 1 week and it is having a short biological half-life, approximately 3-5 h. Therefore, there is a need to once daily controlled release drug delivery systems to extend its therapeutic action entire the day. **Aim:** The main object of the present work deals with the development of pH-independent controlled release tablets of ondansetron HCl using pH modulating technique. **Materials and Methods:** Ondansetron HCl is a weakly basic drug belongs to BCS Class-II and it is showing distinct pH-dependent solubility. The solubility exhibits high solubility at low pH (pH 1.2) at 37°C (23.3 mg/ml); however, it exhibits poor solubility at higher pH (6.8 pH phosphate buffer) at 37°C (0.036 mg/ml). The major limitation of the drug was found burst release in stomach pH 1.2 and highly precipitation in intestinal pH (pH 6.8 phosphate buffer). The formulator is challenging to develop a controlled release formulation of constant drug release in the entire gastrointestinal tract. Matrix tablets were prepared by direct compression technique using high viscosity grade polymer (Methocel K100M), along with pH modifier for the maintenance of constant acidic microenvironment at the surface of the tablet. A 3^2 full factorial design was used to study the effect of pH modulating agent and optimization of ondansetron matrix tablets. Optimized formulation characterized by DSE, X-ray diffraction, and Fourier transform infrared studies was found not having any interaction with polymer and drug. **Results:** The release rates from formulated matrix tablets were studied at (pH 1.2) for 2 h followed by (pH 6.8). Methocel K100M with fumeric acid based matrix tablets effectively overcome pH-dependent solubility, drug release was found to be extended up to 24 h with >90% of drug release; there was a vast different between in the pharmacokinetic parameters, area under the curve, K_e, and T_{max} of the optimized matrix tablets, indicating there comparable controlled pH-independent release effect. It is a potential approach for pH-independent controlled release is well supported by *in-vivo* pharmacokinetic studies. **Conclusion:** The results of in-vivo studies discovered that the optimized formulation with pH modulating agent exhibits a pH-independent controlled release of ondensetron HCl.

Key words: Chemotherapy induced nausea and vomiting, *in-vitro* and *in-vivo* studies, pH independent controlled drug delivery, pH modulating agents, post-operative nausea and vomiting, Methocel K100M

INTRODUCTION

The oral control drug delivery is the most acceptable delivery system for patient acceptance, industrial application and economical but still it has several challenges to design a dosage form. The gastrointestinal pH is one of the foremost limitations for constant drug release due to different pH variations different regions (stomach *vs.* small intestine)

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throughout the gastrointestinal tract (GIT), solubility is one of the major parameters to design controlled released dosage form. Several weakly basic drugs are found to pH-dependent solubility, these drugs are highly soluble at low pH while transfer to high pH 6.8 phosphate buffer it precipitate these precipitate cannot dissolve, Hence, this indicates incomplete drug release results, irregular drug absorption, and fluctuations in plasma concentrations. There is need to develop pH-independent drug release system.[1,2]

The incorporation of pH modulation agents (organic acids) in a high swell able hydroxyl propyl methyl cellulose polymer matrix system is a promising approach, but the selection of pH modifier for a specific drug is not easy. The frequently used pH modifiers are citric acid, tartaric acid, fumeric acid, and tartaric acid. The selection of organic acid was based on their pKa value and solubility. The selection of pH modulating and maintain desire pH for an extended period of drug dissolution is a challenging task for better-controlled drug release. The main object of this research to study the effect of drug release by using Methocel K100M with pH modulating agents.[3]

Ondansetron hydrochloride is a serotonin sub type-3 (5-hydroxytryptamine-3) receptor antagonist. It is an extensively exploit drug for the treatment of several therapeutic purposes like antiemetic especially it is used in the prevention of post-operative nausea and vomiting (PONV) and chemotherapy induced nausea and vomiting (CINV) or radiation induced nausea and vomiting. Ondansetron HCl immediate-release tablets are administered thrice times a day. A controlled release formulation of ondansetrron HCl would enable to control PONV, CINV. A novel advantage improving patient compliance by decreasing multiple drug administration. The usual dose of ondansetron HCl (8 mg) administered is three times a day. By using once daily dose of ondansetron in a single matrix tablet, the drug is released at a slower rate thus extremely preventing nausea and vomiting.[4-6]

This study was designed to formulate matrix tablets of using ondansetron HCl hydrophilic polymer and pH modulating agents containing various concentrations of fumeric acid, Methocel K100M for once a day release of the drug and to make clear the release kinetics, and to determine the various pharmacokinetic parameters were also conducted *in-vivo* pharmacokinetic studies on the optimized formulation was also performed to clarify the possible improvement in oral bioavailability using omeperazole treated rats as a hypochlorhydric condition.[7]

MATERIALS AND METHODS

Ondansetron HCl was obtained from Pranami Drugs Pvt. Ltd., Gujarat; hydroxypropyl methylcellulose (HPMC) (Methocel K100M), Avicel pH 101, lactose and magnesium stearate were supplied by yarrow chemicals, Mumbai, Maharashtra, India. Citric acid, tartaric acid, fumeric acid, and succinic acid were procured from Qualigens Fine Chemicals (Aman Scientific Chemicals Vijayawada, Andhra Pradesh, India. All the other chemicals and reagents used are the high analytical grade respectively.

Solubility of ondansetron HCl

The solubility of ondansetron HCl was determined using simulated gastric fluid (SGF) without enzymes (pH 1.2), pH 6.8 phosphate buffer and pH 7.4 phosphate buffer. The solubility of the active pharmaceutical ingredients (API) was resolute by the equilibrium solubility method. Which employ up to the saturation of a solution to obtain by stirring an excessive of API need to add in the medium until equilibrium is achieved. After equilibrating, the solution was kept in shaker water bath (37 ± 1°C) up to 24 h for maximum solubility of the drug. After that, the samples were removed from shaker bath and filtered with 0.22 µm nylon non-pyrogenic disposable syringe filter. Finally, the filtered solution was diluted and estimated using ultraviolet (UV)-visible spectrophotometer (ELICO SL-210).

Angle of repose

Angle of repose was derived for the powder blend as an indicator for flow ability characteristics. This was determined by a fixed funnel method.[8] The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured, and the angle of repose (q) was calculated using the formula:

$\theta = \tan^{-1}(h/r)$

Differential scanning calorimetric (DSC) studies

To obtain the DSC thermo grams of the drug and their optimized formulations a thermal analysis instrument, Pyres 6 DSC (Jade DSC) was employed. To carry out these studies, 25 mg of drug or formulation of the drug was weighed accurately and placed in one of matched aluminum pans. Both the sample and reference pans were sealed and placed on the heating cell and covered with a glass bell jar. Heating at a rate of 10°C/min with a continuous purge of nitrogen (20 ml/min) was done with recording of energy changes in the sample with respect to the reference in the temperature range of 30-350°C.[9]

X-ray diffraction (XRD) studies

The powder XRD spectra of ondansetron HCl, prepared physical mixtures were obtained using RU-H3R, horizontal rotaflex rotating anode X-ray generator instrument, Rigaku (Rigaku International Corporation, Tokyo). The sample was pressed on a graticule and pressed in such a way that

the sample did not fall on keeping the graticule in vertical position. The graticule was placed in sample holder and exposed to CuKα radiation (40 KV, 50 MA), 2θ=5°-50° scanning speed 3°/min and step size 0.04° 2θ.

Fourier transforms infrared (FTIR) spectroscopy[10]

The infrared absorption spectra of the samples were analyzed using an FTIR spectrophoto meter (SHIMADHU JPN: Registration of utility model No.3116465) pure drug and optimized tablets were prepared by compressing the samples with potassium bromide. The peak variation absorption between 400 and 4000/cm was detected and interpret the result.

Preparation of ondansetron matrix tablets

The entire the tablet formulations with different polymer ratios were prepared by direct compression method. Methocel K100M high viscosity polymer was chosen for its controlled release property. Methocel K100M, fumeric acid, avicel pH101, and polyvinylpyrrolidone were physically blended until a homogeneous mixture was obtained composition as shown in Table 1. Magnesium stearate and talk was then added and mixed for 1 min. Cadmach tablet machine was used to compress tablets of about 300 mg average weight and 4.5 mm thickness using concave punches of 8 mm diameter.[11]

Evaluation of tablets

Hardness test

The hardness of matrix tablets was determined using Pfizer hardness tester. From each formulation batch, three matrix-tablets were randomly taken and the values were calculated.

Friability test

The test was performed by initially weighing 5-tablets and then transferring into VEEGO friabilator. The friabilator was operated at 25 rpm for 100 revolutions and the matrix-tablets weighed again. Friability was computed as percent loss in weight.

Table 1: Preliminary formulations of ondansetron without pH modulating agents

Ingredients	Formulation			
	F1	F2	F3	F4
Ondansetron HCl	25	25	25	25
Methocel K100M	25	50	75	100
PVP	5	5	5	5
Lactose	190	165	140	115
Talc	2.5	2.5	2.5	2.5
Mg stearate	2.5	2.5	2.5	2.5
Total weight	250	250	250	250

PVP: Polyvinylpyrrolidone

Weight variation test

From each formulation batch, 10 matrix-tablets were randomly taken and weighed individually to determine variation.

Uniformity of thickness

From each formulation batch, six matrix-tablets were randomly taken and measured for thickness using a micrometer screw gauge.[12,13]

Drug content uniformity

For estimation of drug content the first two tablets were taken and then crushed into fine powder in the mortar. Then, this fine powder equivalent to 25 mg of ondansetron was extracted in pH 6.8 phosphate buffer. This solution was filtered through a Millipore filter of 0.45 µm pore size. After suitable dilutions, drug content was spectrophotometer determined at a wavelength of 249 nm.

Dissolution studies

The *in-vitro* drug release study was conducted using USP Type-II, rotating paddle apparatus (VEEGO Instruments Corporation, Mumbai, India). The operating speed was at 50 rpm. SGF (pH 1.2, 900 ml) was used as dissolution medium for first 2 h and pH 6.8 phosphate buffer was used for the remaining test period. The temperature was maintained at 37 ± 0.5°C. Simultaneously, we studied both pH 1.2 and 6.8 continuously for complete drug release study. Samples were withdrawn at pre-determined time intervals, filtered, and analyzed using UV-visible spectrophotometer (ELICO SL-210) at 249 nm.[8]

In-vivo study

A total of 30 Wistar albino rats are dividing into six groups, each group containing five rats. Group I: Market available vomikind (ondansetron 4 mg), Group II: pH modifier ondansetron 4 mg, Group III: Without pH modifier of ondansetron 4 mg, Group IV: Omeprazol induced hypochlorohydria with pH modifier, ondansetron 4 mg. Group V: Omeprazol induced hypochlorohydria without pH modifier, ondansetron tablet 4 mg. Group VI: Omeprazol-induced hypochlorohydria of market available vomikind (ondansetron 4 mg).[10,14]

Selection of experimental design

A 3^2 factorial design was selected for the study. Two main factors, i.e., the concentration of the polymer and ratio of

pH modifier were evaluated at different 9 combinations. Three levels of the factor X_1 (concentration of HPMC K100M) and X_2 (acidifier) selected to find out its effect on drug and acidifier release. While ratios of polymer and pH modifier at three levels were selected to identify separate as well as combined effects of both controlled released polymer (HPMCK100M) and pH modifier (fumeric acid). Percentage of drug release after 2 h (>20%) and percentage of drug release after 20 h (<90%) were selected as dependent variables. In this design, two factors were studied at three levels and experimental trials were performed at all nine possible combinations. An additional formulation without any acidifiers was also formulated for comparative drug release study (F0). The composition of the 3^2 full factorial design investigated is shown in Table 2.

Administration and sampling protocol

The study protocol was approved by the Institutional Animal Ethics Committee (VIKAS/AEC/2014/001/CPCSEA) approved the protocol of the study. Healthy male Wistar albino rats weighing between 300 ± 23 g and 350 ± 23 g were used. Rats were separated into six groups, each consisting of five rats. Group I: Market available vomikind (ondansetron 4 mg), Group II: pH modifier ondansetron 4 mg, Group III: Without pH modifier of ondansetron 4 mg, Group IV: Omeprazol induced hypochlorohydria with pH modifier of ondansetron 4 mg. Group V: Omeprazol induced hypochlorohydria without pH modifier, ondansetron tablet 4 mg. Group VI: Omeprazol induced hypochlorohydria of market available vomikind (ondansetron 4 mg). The dosage form was given orally via silicone rubber gastric intubation tube. All the rats were housed in individual cages at room temperature, fasted before the 12 h of drug administration and have access to water and food after 4 h of dosing throughout the study period. Approximately, 0.5 ml of blood sample was collected at proposed time points such as pre-dose, 1.3, 6, and 12 h through a retro orbital route. All the blood samples were collected into K_2 ethylenediaminetetraacetic acid coated tubes. Samples were centrifuged at 4000 rpm for 5 min. The plasma was separated and stored at −70°C until analysis.[15]

Table 2: 3^2 full factorial design

Formulation code	Coded values	
	X_1	X_2
F1	−1	−1
F2	−1	0
F3	−1	1
F4	0	−1
F5	0	0
F6	0	1
F7	1	−1
F8	1	0
F9	1	1
Translation S of coded values to actual values		
Coded values	−1	0	1
Methocel K100M	50	75	100
Fumeric acid	15	30	45

Determination of ondansetron HCl from plasma

The reverse phase high performance liquid chromatography method was used for the estimation of ondansetron HCl from rat plasma and Ondansetron HCl used as an internal standard. The 0.01 M potassium dihydrogen phosphate, acetonitrile, and methanol (55:22.5:22.5) as an eluent. The eluent was detected at 247 nm.[16,17]

Pharmacokinetic analysis

The pharmacokinetic study was carried out to determine the various parameters such as time to reach maximum concentration (T_{max}), maximum plasma concentration (C_{max}), and the area under the curve (AUC0-inf). The values of T_{max} and C_{max} were noted from the arrhythmic plot of time versus plasma concentration of ondansetron HCl. The AUC was determined by trapezoidal rule.

RESULT AND DISCUSSION

pH-dependent release of weakly basic drug

From the solubility study, it was found that 100% drug was released for pure ondansetron HCl in SGF pH 1.2 within 10 min but in 6.8 pH phosphate buffer; the drug was immediately precipitated and it formed large crystals.[10] A large variation in drug release was observed in pH 1.2 and 6.8 pH phosphate buffer. Drug release is shown in Figure 1.

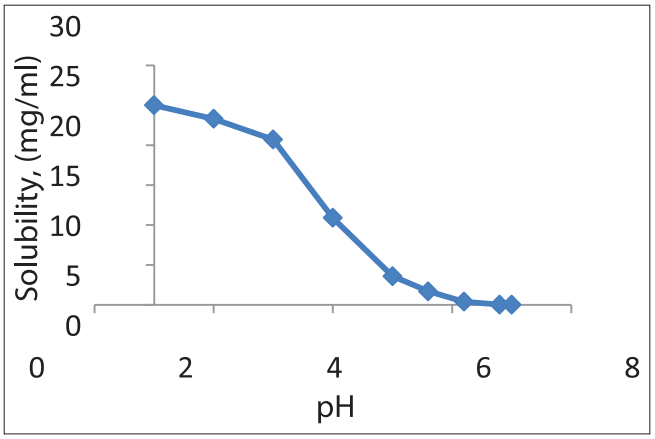

Figure 1: pH solubility profile of ondansetron hydrochloric acid at 37°C

Flow property of the blend (angle of repose)

Before compression, all the formulations were evaluated for their flow property. From the values of Angle of repose, it is clear that blends having Methocel K100M with fumeric acid formulation is showed better flow property. The formulation containing Methocel K100 (F1-F4) property was falling in the passable range, flow property was falling in the excellent, in which values of angle of repose were found to be 24.23 ± 0.32 and 26.45 ± 0.19, respectively.

FTIR spectroscopy studies

The FTIR of ondansetron HCl and polymer mixtures and optimized matrix tablets dosage form studied by KBr pellet technique. The ondansetron HCl exhibited characteristic peaks at 3,394 and 1,633 cm, attributed to O-H stretching and C=O stretching vibrations. The physical spectrum not showed significant shift in peaks of ondansetron HCl and somewhat change some intensity peaks were found. And as well as optimized formulation Methocel K100M with fumeric acid formulation were studied the band at 3,499 cm for O-H stretching and 1,699 cm for C=O stretching were found. The results of IR spectroscopy reveal that there was no chemical interaction between ondansetron and Methocel K100M with fumeric acid combination of polymers. IR spectra were shown in Figures 2 and 3.

XRD analysis

XRD the freshly prepared powdered samples under controlled temperature and humidity conditions were record at room temperature on XRD meter with Cu Ka radiation (1.54 Å), at 40 kV, 30 mA, passing through a nickel filter with a divergence slit (0.5°), anti-scattering slit (0.5°), and receiving slit (1 mm). The presence of many diverse peaks in the XRD pattern indicate that ondensetron HCl API crystalline material with characteristic diffraction peaks appearing at a diffraction angle of 2θ at 10.2, 19.2, 22.5, 29.11, and 35.6. Optimized formulation containing Methocel K100M with fumeric acid exhibits a distinct pattern with diffraction peaks at diffraction angle of 2θ at 7.82, 15.99 and 22.5. The diffraction pattern of placebo was found to differ in comparison with drug. Some peaks were disappeared, some peaks were appeared, and some peaks heights were decreased. Taken as a whole diffraction pattern revealed that there is no change in polymorphic properties of the drug and the drug is well distributed throughout the preparation of optimized formulation (F8); XRD results were shown in Figure 4.

DSC study

DSC study was perform on the pure ondansetron HCl, and optimized formulation with Methocel K100 and fumeric acid used in the study the drug-polymer complex to access whether there is any interaction between drug and polymer. The thermo gram of pure ondansetron gave a melting endothermic at 203.25°C. The thermo gram of optimized formulation gave the same melting endoderm 213.25°C. So from the DSC curve, it has been confirmed that there is no change in endothermic peak of the drug. And hence, the drug and polymers are well compatible with each other. (15) DSC of spectrum was shown in Figure 5.

Tablet assay and physical evaluation

The drug content in studied formulations varied between 96.2 and 101.7% (mean ± SD = 98.8 ± 1.6%). Average weights of the tablets of different batches varied between 298.5 and 278.7 mg (mean ± SD = 249.6 ± 1.83 mg). Hardness and friability of the tablets ranged from 5.6 to 6.4 kg/cm^2 (mean ± SD = 5.6 ± 0.8 kg/cm^2) and 0.3-0.73% (mean ± SD = 0.52 ± 0.13%), respectively. Thickness and diameter were not more than 5% of the average value. These results show that all physical parameters of the compressed matrices were within the permissible limits of USP.

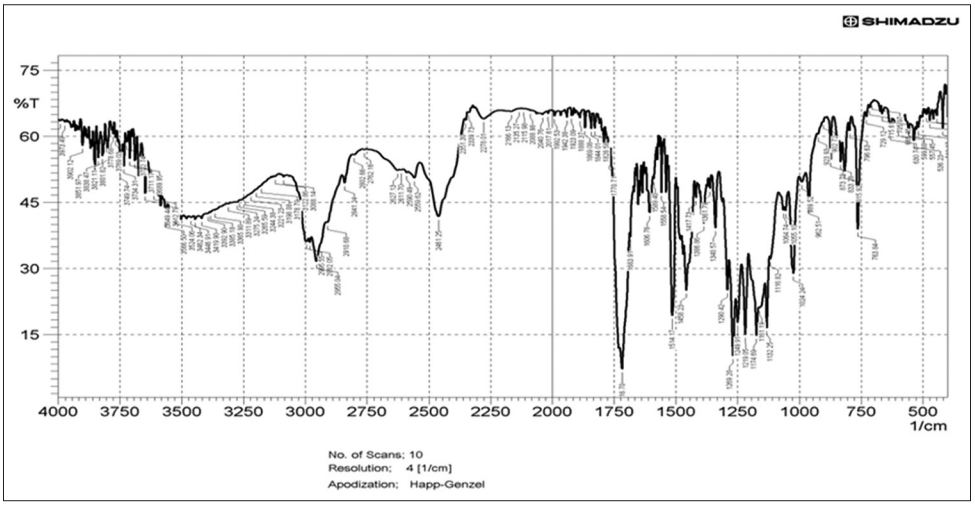

Figure 2: Fourier transforms infrared spectra of ondansetron HCl

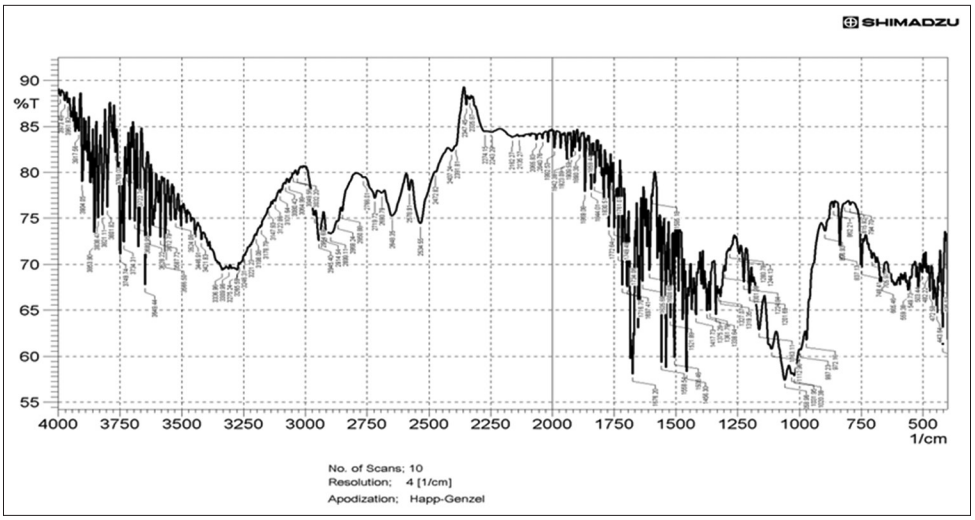

Figure 3: Fourier transforms infrared spectra of optimized formulation (F8)

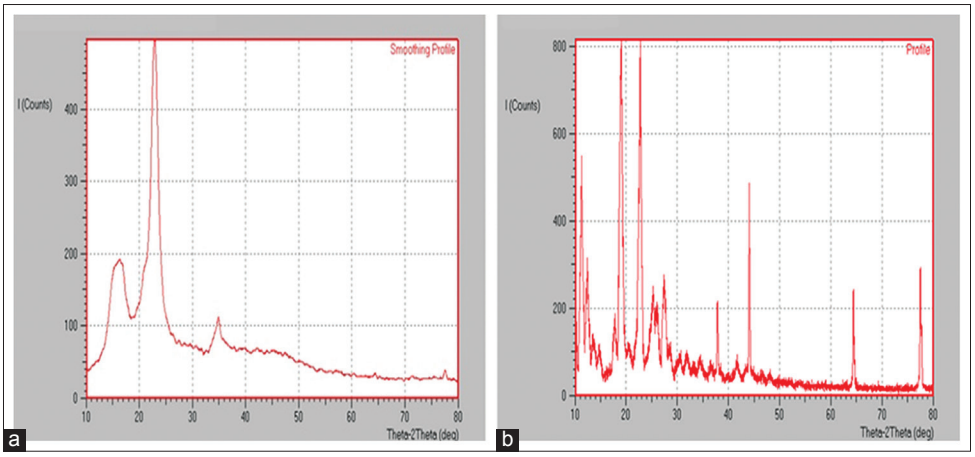

Figure 4: (a) X-ray diffraction (XRD) results of ondansetron pure drug, (b) XRD results of optimized formula

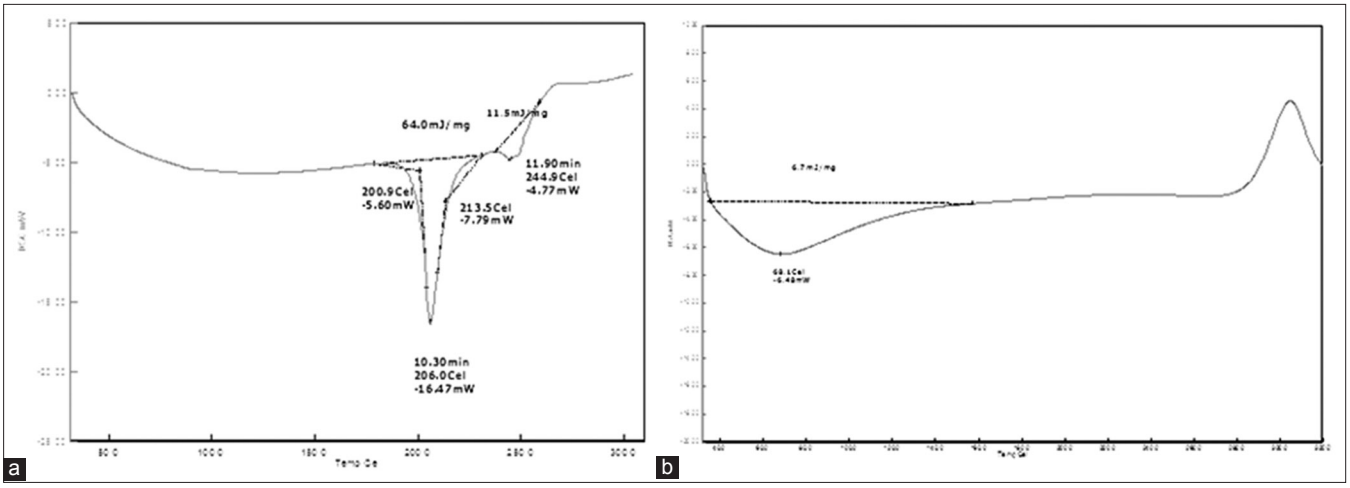

Figure 5: (a) Differential scanning calorimetric of spectrum of ondansetron, (b) DSE spectrum of optimized formula

pH-dependent release of weakly basic drug

The matrix forming polymer HPMC K100M was selected for its release controlling ability, matrix gel layer characteristics and its viscosity are pH independent. The formulations were designed in different concentrations of polymer. The matrix forming the tablets were studied in different pH mediums, a remarkable difference in the

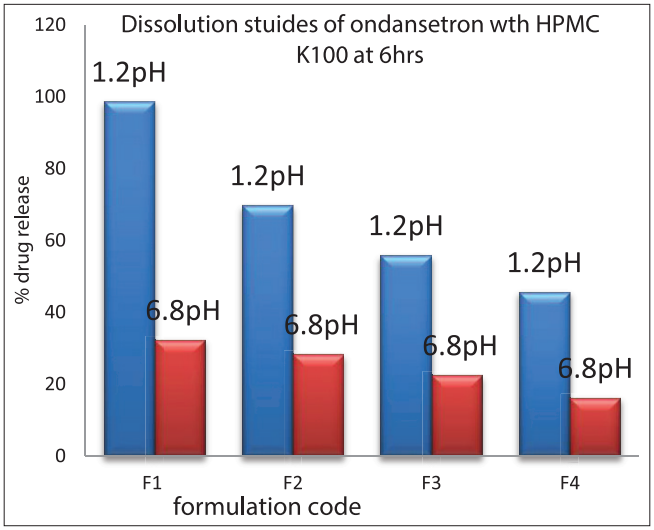

Figure 6: pH dependent release of ondansetron HCl from hydroxypropyl methylcellulose matrix device

drug release was observed in pH 1.2 SGF and pH 6.8 phosphate buffer. The drug release from the matrix tablet in pH 1.2 was relatively faster from all the formulations but different in pH 6.8 phosphate buffer. The result was found low concentration of polymer burst release was observed in SGF pH 1.2, consequently, precipitation was observed in pH 6.8 phosphate buffer. When formulation containing with optimized concentration of Methocel K100M (F4, 1:4 ratio), approximately 22.24% in pH 1.2 after 2 h and 64% of drug release in 6.8 phosphate buffer after 24 h, respectively. It was showed incompletely drug release and drug was not released complete from matrix device pH-dependent drug release was found the drug released was shown in Figure 6.

Optimization data analysis

To find out optimized batch based on set criteria, 3 × 2 full factorial design was applied. From the data obtained for factorial batches, ANOVA was performed to evaluate responses by a statistical model incorporating polynomial and interactive terms:

$$Y=\beta_0+\beta_1X_1+\beta_2X_2+\beta_3X_3+\beta_{12}X_1X_2+\beta_{23}X_2X_3+\beta_{31}X_3X_1 +\beta_{123}X_1X_2X_3$$

Coefficients of above equation were calculated and following reduced mathematical models were derived using MLRA for studied responses. A level of significance was set at 5%. The polynomial equation (Q2) suggests linear model while second equation (Q24) illustrate 2FI model. Coefficients for intercept, first order effect and interaction terms in above equations reveal their significance by their indication and magnitudes. The negative values obtained for coefficients of factor X_1 (HPMC K100M) exposes its negative effect on both the responses. While the positive values obtained for coefficients of factor X_2 (acidifiers ratio) exposes its positive effect on both the responses. Besides positive interaction term in the second equation also shows positive influence on the response Y_2. As the amount of factor X_1 (HPMC K100M) increases, amount of Q2 decreases; but contrary to it, increasing amount of factor X_2 increases value of Q2. A similar pattern is observed for response Q24 but in more pronounced manner. It is assured that factor X_2 (fumeric acid) has more influence on the responses than factor X_1.

Effect of pH modifiers on drug release profile from matrix tablets

Incorporation of pH modifier is a common strategy to enhance the drug release rate of pH-dependent weakly basic drugs. These pH modulating agents having ability to alter the micro environmental pH in the surface of the tablet and surrounding dissolution media. These agents are having ability to maintain constant pH for during the entire period of the drug release.The addition of pH modulating (fumeric acid) in a HPMC matrix device was found the drug release was increased in 6.8 pH phosphate buffer. The selection of organic acid was based on their pKa value and solubility. All the formulations showed almost similar drug release profiles in acidic dissolution media. While drug release decreased gradually in alkaline media. This type of behavior may be attributed to acidic environment created by acidifier and dissolution of drug present in outer part of the matrix. Thereafter, drug release was decreased by gradual loss of acidifier and swelling of polymer matrix. Drug release profiles of different formulations. Surface pH of different formulations with respect to time solely dependent on pH Modifier created by acidifier. All three formulations (F1, F2, and F3) showed improvement in drug release as compared to the formulation without pH modifier (F0). However, high concentrations of drug release was found in the first 2 h in SGF pH 1.2 (<20%) results was shown in Table 3. As per the drug release profile the object depicted from all the formulation F8 (fumeric acid (10%) with high concentration of HPMC100M) was optimized, it can maintain constant drug release for extended period up to 24 h compared to remaining formulations. In conclusion the addition of pH modulating agent to HPMC matrix tablets was found satisfactory results to achieve pH independent drug release. Further *in-vitro* - *in-vivo* study was developed non-gastric resident ondansetron to correlate *in-vitro* - *in-vivo* studies in hopochlorhydria conditions. Optimized formulation drug release profile has shown in the Figure 7.

Effect of surface pH of tablet

The determination of surface pH is one of the major parameters either the HPMC drug device is maintaining the constant surface acidic pH of the tablet in 6.8 phosphate buffer for prolonged time. For this study, two

Table 3: Dissolution parameters of various matrix tablet formulations prepared as per the experimental design

Batch code	Transformed values		Drug release response %	
	X_1	X_2	Y_1 (First 2 h)	Y_2 (20 h)
F1	−1	−1	45±0.2	85±0.3
F2	−1	0	40±0.3	80±0.2
F3	−1	+1	38±0.1	84±0.3
F4	0	−1	40±0.3	89±0.2
F5	0	0	35±0.2	90±0.3
F6	0	+1	30±0.1	94±0.2
F7	+1	−1	25±0.2	85±0.1
F8	+1	0	19±0.3	91±0.1
F9	+1	+1	25±0.1	96±0.2
F0	Without pH modulating agent of optimized formula		10±0.4	50±0.3

Table 4: Pharmacokinetic parameters of ondansetron HCl matrix tablets for oral administration in normal and omeprazole treated rats

Pharmacokinetic parameters	Normal rats			Omeperazole induced rats		
	Vomikind	F8 (with pH modifier)	F0 (without pH modifier)	F8 (with pH modifier)	F0 (without pH modifier)	Vomikind
C_{max} (ng/ml)	240.01±10	356.09±10	224.35±8	587.27±7	665±11	432.48±12
T_{max} (h)	6±0.2	1±0.2	1±0.3	6±0.3	12±0.4	1±0.5
Ke (h^{-1})	0.020727	0.218	0.0336	0.101	0.07599	0.193
$t_{1/2}$ (h)	33.43±0.3	3.167±0.2	20.61±0.2	6.83±0.3	9.11±0.2	3.58±0.1
AUC (ng/h/ml)	1381.98±55	993.68±44	890.86±143	3210.52±78	14076.5±76	5126.24±78

AUC: Area under the curve

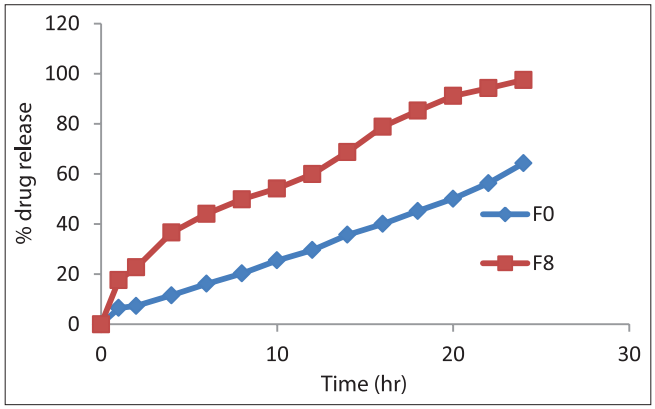

Figure 7: Drug release profile of optimized formulation compared with pH modulating agent (F8) and without pH modulating agent (F0)

techniques were used one is common technique to take 20 ml phosphate buffer in a Petri dish and tablet was immersed in the Petri plate at the surface of tablet dipped pH electrode and it will show the surface pH of the tablet. The optimized formula (F8) was found for prolonged drug release time acidic pH was maintained at the surface of the tablet.

Pharmacokinetic profile of ondansetron optimized formulation

The rats were treated with 30 mg/kg omeprazole to maintain hypochlorhydria entire GIT and another group without omeprazole, pharmacokinetic behavior of ondansetron was studied. After oral administration of ondansetron without pH modulating agent (F0) and with pH modulating agent (F8) consequently compared with marketed vomikind (4 mg). Products were studied in normal rats to compare the pharmacokinetic behavior of ondansetron with omeprazole treated rats. Figure 8 shows the plasma concentration and time profile of ondansetron in rats after oral administration and relevant pharmacokinetic parameters such as maximum concentration (C_{max}), maximum time (T_{max}), half-life, and AUC are given in Table 4. The result was found after oral administration of ondansetron in omeprazole treated rats was found to be much lower than that in normal rats. In case the optimized formulation with pH modulating agent higher plasma concentration was found in omeprazole induced rats with sustained release. The C_{max} values of optimized formulation in the omeprazole induced without pH modulating agent treated rats was 240 ± 3.4 ng/ml and omeprazole induced with pH modulating agent was

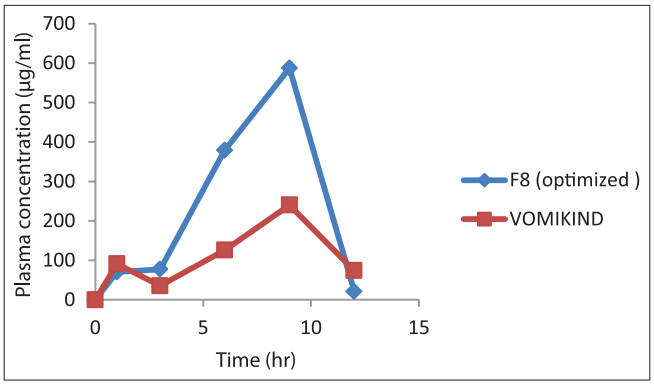

Figure 8: Comparative *in-vivo* pharmacokinetic study of optimized matrix tablets (F8), and marketed product (vomikind) studied with omeprazole induced rats

432 ± 3.3 ng/ml. The optimized formulation *in-vivo* results were revealed improved pH dependent dissolution behavior with pH modulating agent technique.[18-23]

CONCLUSION

In this study, pH independent controlled release matrix tablets of ondansetron HCl with enhanced dissolution and bioavailability were prepared successfully by incorporating a pH modifier in a matrix tablets. Physical and pharmacokinetic parameters were determined on the basis of obtained results and it was concluded that the F8 was optimized polymer concentration for pH independent controlled drug release up to 24 h, in the pharmacokinetic study by using omeprazole induced rats to maintain hypochlorhydric condition.

The *in-vivo* studies clearly indicated that pH modifier approach can be adopted for the formulation of matrix tablets to achieve a pH independent drug release. *In-vivo* pharmacokinetic studies in rats confirmed the prolonged release by showing an increase in bioavailability of ondansetron HCl.

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